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Editorial

Primary Biliary Cirrhosis: Present and Future

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Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by progressive destruction of the small intra-hepatic bile ducts and the development of portal and periportal inflammation, leading to cirrhosis. There is a close association between PBC and antibodies to pyrubate dehydrogenase complex (antimitochondrial antibodies - AMA).

Population based studies have estimated the incidence of PBC as 19.1-251/1,000,000 in the general population. The disease was originally described as being associated with severe progressive cholestasis manifested by jaundice, xanthoma, pruritis, melanodermia, clinical features of portal hypertension and liver failure. The spectrum of the disease has changed markedly in the last few decades as a result of the early detection of AMA. Currently the typical patient with PBC is a middle-aged woman without symptoms or with only fatigue and itching. The overall survival rate in symptomatic patients ranges from 5 to 15 years.[1] There are several prognostic models for predicting survival, with serum bilirubin level being the only one common to all of them. The prognosis appears to be different among symptomatic and asymptomatic patients. However, it is evident that even the asymptomatic patients have a shorter survival compared to the general population.[2] Furthermore, there is evidence suggesting that the distinct serological features of AMA-negative PBC are not associated with substantial differences in the clinical spectrum or course of the disease.[3]

The pathogenesis of PBC remains uncertain. The disease has been considered as an example of autoimmunity. There no evidence as yet that the AMA are implicated in the pathogenesis of PBC. Immunization of animals with E2 results in the generation of AMA but no bile duct lesions are seen. A variety of agents have been suggested to trigger PBC including the bacteria Escherhia coli and Mycobacteria gordonae, but convincing evidence is still lacking. Presence of a raised familial risk for primary biliary cirrhosis could be an indirect link to a genetic component for disease susceptibility. Results of studies have estimated frequency of the disease among first-degree relatives of index cases to be between 1.3-6%. The increased rate of PBC in first degree relatives is based on a predominance of mother/daughter relationships.[4]

Despite the considerable number of trials which have dealt with the treatment of PBC, it is still debated whether current therapies are effective in improving the natural history of the disease or in preventing the disease and its complications. The immunologic theories of the pathogenesis of PBC have led to the use of azathioprine, cyclosporine and methotrexate for the management of these patients without success.[5] Though corticosteroids have also been evaluated, they have not been used because of the complication of osteoporosis.

Recently budesonide was suggested, but this oral corticosteroid, eliminated on first pass through the liver, appears also associated with worsening osteoporosis in patients with PBC. In an attempt to reduce fibrinogenesis colchicine monotherapy has been used but has shown no benefit.

Therapy with ursodeoxycholic acid (UDCA) could have a beneficial role in the progression of PBC, as it seems to have a cytoprotective effect, modifying the immune system and suppressing the bile acid cytotoxicity. Five randomized controlled trials of adequate size and duration have provided information about the effectiveness of UDCA in primary biliary cirrhosis. Collectively, these studies randomized 890 individuals to either ursodiol or placebo and followed them for an average of two years. The dose regiment in these studies varied from 10

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to 15 mg/Kg. In all trials, UDCA produced a rapid and impressive improvement in serum liver tests, particularly alkaline phosphatase, bilirubin, aminotransferases, and IgM levels. Four of the five trials reported beneficial effects on histology, primarily improvement in inflammatory feautures, and less ductopenia in the treated groups. However, it is clear from the histological data obtained in these trials that the ongoing destruction of bile ducts is not completely halted by UDCA. No effect on the development of cirrhosis, portal hypertension, or death/transplantation could be detected at 2 years in any of the individual trials. However, in follow-up of one of the study groups, UDCA therapy was associated with a delay in the onset of varices. In addition, results of a combined analysis of three studies that used ursodeoxycholic acid at 13-15 mg/Kg per day showed improvements in survival without liver transplantation in patients receiving the active drug. Long term (10 year) survival with UDCA has also been noted to exceed that predicted in a selected population.[6-8] Nevertheless, the positive effects of UDCA on disease progression and survival without need for liver transplantation have been extensively questioned in two large, well conducted meta-analyses.[9,10] Both meta-analyses were unable to demonstrate a significant effect of UDCA on the incidence of death, liver-related death, death or liver transplantation, and complications of liver disease based on an analysis of data before and after the patients had been switched on to open label UDCA. In addition, pruritus, fatigue, autoimmune conditions, quality of life, liver histology, and portal pressure were not significantly affected by UDCA. On the other hand, both reviews confirmed and extended previous observations showing a beneficial effect of UDCA on a number of liver biochemical variables, including serum bilirubin concentration and serum enzyme activities, jaundice and ascites in PBC patients. This lack of firm clinical evidence for an effect of UDCA in PBC on clinically important outcome variables does not necessary mean that UDCA is not of any help in patients with PBC. Further meta-analyses based on individual patient data, including subgroup analyses, ought to be performed in order to identify subgroups of patients who may benefit from UDCA. If one could obtain individual patient data from all RCTs treating patients with UDCA versus placebo or no-intervention, analyses adjusting for prognostic variables might reveal important information. Such analyses could perhaps identify subgroups of PBC patients with the best chance of benefiting from UDCA treatment. The drug is safe and well tolerated. The primary limitations associated with UDCA are its cost and need for long term treatment. Trials with combination therapies such as mycophenolate mofetil (MMF) and UDCA, silymarin and UDCA and Bezafibrate and UDCA have been reported but to date these therapies are not recommended.

Liver transplantation seems to be the only treatment for patients with end stage disease and intractable symptoms.[11] The cumulative risk of recurrent disease has now been estimated at 15% at 3 years and 50% at 10 years with granulomatus cholangitis being the histological hallmark of the disease in the native liver. The appearance of serum mitochondrial antibodies seems to be independent of recurrence risk. These antibodies could disappear soon after liver transplantation only to return later, with or without recurrent disease. There are no factors which clearly predict those patients who are at risk of recurrent disease and therefore there is, at present, no way of preventing disease recurrence. However, several studies have suggested that recurrent disease is more common and is detected at an earlier stage in those who are receiving tacrolimus-based immunosuppression rather than cyclosporine-based immunosuppression. Thus, there may be a rationale for offering these patients cyclosporine-based treatment. No information is available about the efficacy of UDCA treatment in halting disease progression from recurrent primary biliary cirrhosis.

Because the etiology of PBC is still unknown, therapies remain empirical and management should focus on the symptoms and complications of PBC, such as pruritis, osteopenia and portal hypertension.[12] No contributions on preventative therapy supported by evidence-based medicine have been published so far. AMA positive patients with normal liver enzymes and patients transplanted for PBC with no signs of recurrence of the disease may be considered for preventative treatment.

The biggest impediment to improving the diagnosis and treatment of patients with PBC remains its elusive pathogenesis. Several critical issues must be answered in the immediate future. Definitely we have to clarify, what defines the genetic susceptibility to the disease? Which genes are important in the pathophysiology of PBC? Why does PBC primarily affect women? Why does PBC localize to small bile ducts and salivary ducts? What causes the development of anti-mitochondrial antibodies? The answers to these questions are key to understanding the pathogenesis of PBC and improving the management of these patients. Gene therapy may prove to be an exciting therapeutic option in the management of these patients. Although the study of PBC is significantly retarded by the lack of an adequate animal model, the molecular technology to address these issues is advancing rapidly. With the advent of these tools, investigators are well

poised to address the important issues of PBC in the future.

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